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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte AUDREY GODDARD, PAUL J. GODOWSKI, AUSTIN L. GURNEY, MELANIE R. MARK, and RUEY-BING YANG

Appeal 2008-2163
Application 09/202,054
Technology Center 1600

Decided: May 1, 2008

Before TONI R. SCHIENER, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

Opinion for the Board filed by *Administrative Patent Judge* ERIC GRIMES.

Opinion Concurring-in-part and Dissenting-in-part filed by *Administrative Patent Judge* JEFFREY N. FREDMAN.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to an antibody that binds a specific human protein. The Examiner has rejected the claims as lacking utility, anticipated, and obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse the rejections for lack of utility, but affirm the prior art rejections.

BACKGROUND

"The *Drosophila* . . . Toll protein controls dorsal-ventral patterning in *Drosophila* embryos and activates the transcription factor Dorsal upon binding to its ligand" (Spec. 1-2). "In adult *Drosophila*, the Toll/Dorsal signaling pathway participates in the anti-fungal immune response" (*id.*).

The Specification states that five human homologues of the *Drosophila* Toll protein, designated huTLRs1-5, have been cloned (*id.* at 2: 23-24). A constitutively active mutant of TLR4 has been shown to "induce the activation of NF-κB and the expression of NF-κB-controlled genes for the inflammatory cytokines IL-1, IL-6 and IL-8. . . . It has been suggested that Toll functions in vertebrates as a non-clonal receptor of the immune system, which can induce signals for activating both an innate and an adaptive immune response in vertebrates." (*Id.* at 2: 8-14; 2: 26-28.)

The Specification discloses cDNAs encoding human proteins designated PRO285, PRO286, and PRO358. "[I]t is presently believed that the PRO285, PRO286 and PRO358 proteins . . . are newly identified human homologues of the *Drosophila* protein Toll" (*id.* at 16: 3-5). "PRO285, PRO286, and PRO358 may be involved in inflammation, septic shock, and response to pathogens. . . . The role of PRO285, PRO286 and PRO358 as pathogen pattern recognition receptors, sensing the presence of conserved molecular structures present on microbes, is further supported by data . . . showing that a known human Toll-like receptor, TLR2 is a direct mediator of LPS signaling" (*id.* at 16: 6-12).

DISCUSSION

1. CLAIMS

Claims 28-30, 48-50, and 54-57 are pending and on appeal. Claim 55 is representative and reads as follows:

> 55. An isolated antibody which bind to a PRO285 polypeptide comprising:
> (a) amino acids 1 to 1049 encoded by SEQ ID NO:2, or
> (b) amino acid residues 20 to 836 of SEQ ID NO:1;
> wherein the antibody is an agonist or an antagonist of NF-κB activation.

2. UTILITY

Claims 28-30, 48-50, and 54-57 stand rejected under 35 U.S.C. §§ 101 and 112, first paragraph, on the basis that the Specification does not disclose a patentable utility for the claimed antibodies (Ans. 3, 6). The Examiner cites Jurk[1] as evidence that "even four years after the filing date of the instant application, the biological function of PRO285, by applicants['] later designation TLR7, was unknown" (Ans. 3). "Thus, even four years after the filing date of the instant application, the role of TLR7, aka PRO285, was unknown, and the receptor was merely a subject for further research" (*id.* at 4).

The Examiner also states that the asserted "utilities are predicted based upon predicted properties of anti-TLR2 antibodies, on the basis that PRO285 shares (an unspecified amount) of homology with TLR2. . . . It is noted that when the sequence of PRO285 was searched against all available databases, that *no significant homology to TLR2 was detected*" (*id.* at 4-5).

[1] Jurk et al., "Human TLR7 or TLR8 independently confer responsiveness to the antiviral compound R-848," *Nature Immunology*, Vol. 3, pp. 499-500 (2002).

The Examiner concludes that the "specification provides the sequence of a protein, and then goes on to invite the reader to find out what the biological significance of the protein is," and therefore does not disclose a patentable utility for the claimed antibodies (*id.* at 6).

Appellants argue that the evidence in the Specification and evidence provided by way of a declaration under 37 C.F.R. § 1.132 support the asserted utility of the claimed antibodies in treating septic shock (App. Br. 7-10; Reply Br. 6-9).

We conclude that the Examiner's rejections are not supported by a preponderance of the evidence of record. The Specification states that the "primary function of the family of Toll receptors is believed to be to act as pathogen pattern recognition receptors sensing the presence of conserved molecular pattern[s] present on microbes" (Spec. 37: 12-14). Based on this function, the Specification states that "anti-Toll receptor antibodies . . . might be useful in the treatment of septic shock" (*id.* at 37: 24-25).

Evidence to support this function of the TLR family proteins is provided in the Specification's Example 11 (*id.* at 48-53), which shows that TLR2 activates NF-κB in response to bacterial lipopolysaccharide (LPS), as well as the disclosure in the prior art (discussed in the Specification at 2: 3-11) that a constitutively active mutant of TLR4 activates NF-κB, which induces inflammatory cytokines.

Appellants also provided evidence to support their position in the form of a declaration under 37 C.F.R. § 1.132 by J. Fernando Bazan. Dr. Bazan states that he was a co-author of a paper[2] that compared the sequences

[2] Rock et al., "A family of human receptors structurally related to *Drosophila* Toll," *Proc. Natl. Acad. Sci. USA*, Vol. 95, pp. 588-593 (1998).

of TLRs1-5 and that noted that the finding that TLR4 activates NF-κB was expected based on the homology data (*id.* at ¶¶ 6, 7). Dr. Bazan concludes that, based on the evidence of record and the state of the art, "one skilled in the art would reasonably understand that PRO285 can induce the activation of NF-κB and/or the expression of NF-κB-controlled genes and that antibodies to PRO285 could be made and used in accordance with routine technique to modulate such activity" (*id.* at ¶ 8).

Dr. Bazan also points to the Specification's disclosure of a stretch of thirteen amino acids at the C-terminus of TLR2 that is said to bear "striking similarity" (Spec. 51: 21) to a region of the Interleukin-1 receptor (Bazan Decl. ¶ 4). The Bazan declaration provides a comparison of the TLR-2 and IL-1R sequences with the corresponding sequence from PRO285, which shows a very similar sequence (*id.* at ¶ 4). Dr. Bazan points to data provided in the Specification's Example 11 showing that when only this stretch of thirteen amino acids is deleted from TLR2, the resulting deletion mutant cannot activate NF-κB (*id.* at ¶ 5).

The Examiner discounts the importance of the thirteen-amino-acid stretch of PRO285, on the basis that the Specification's Figure 7B, which shows "an alignment of IL-1R with TLR2 in the region critical for IL-1R signaling . . . reveals that six residues are indicated as being 'essential for IL-1R signaling', and only three of those six are conserved in TLR2" (Ans. 15).

In our view, the evidence provided in the Bazan Declaration further supports the utility asserted for the claimed antibodies. The Specification states that a stretch of thirteen amino acids in the interleukin-1 receptor (IL-1R) is "critical for IL-1R . . . signal transduction" (Spec. 7: 13) and required

for association with the protein IRAK. This characterization is supported by Rock, which states that this segment ("Block 10" in Fig. 2) is the location of six out of seven "deleterious mutations" in IL-1R (figure legend for Fig. 2). The amino acids indicated by Rock to be the sites of "deleterious mutations" are the same ones that are described as "essential for IL-1R signaling" in the Specification (Spec. 7: 15). They are not, however, invariant among members of the TLR and IL-R families (Rock, Fig. 2). Thus, those skilled in the art would understand that the Specification's description of them as "essential" applies to IL-1R, not to all related proteins. We do not agree with the Examiner's conclusion that the lack of an exact match in PRO285 for all six of the "essential" amino acids means that PRO285 is likely to lack NF-κB activating function.

In our view, the high degree of sequence similarity shared by the thirteen-amino-acid stretches of IL-1R, TLR2, and PRO285, combined with the description of that segment as critical to function of IL-1R (Spec. 7: 13; Rock, Fig. 2) and the Specification's data showing that deletion of only that segment of TLR2 abolished NF-κB activating function, supports the Specification's assertion that PRO285 is involved in the inflammatory response to pathogens; e.g., the activation of NF-κB and induction of expression of NF-κB-controlled genes like IL-1, IL-6, and IL-8.

In our view, the Examiner's focus on whether the natural ligand of PRO285 is known (Ans. 3-4) misses the mark. The evidence of record supports the Specification's assertion that a primary function of the TLR family is as "pathogen pattern recognition receptors" that sense pathogen-specific products such as LPS. Sepsis is a result of an inflammatory

response to a pathogen, and the evidence of record shows that TLRs would be expected to be among the signaling proteins that trigger an inflammatory response in reaction to a pathogen-specific product. Thus, those skilled in the art would expect that down-regulating the activity of a TLR family member like PRO285 would be useful in treating sepsis regardless of which specific pathogen-specific product is triggering the body's reaction.

The Examiner's rejections based on lack of patentable utility are not supported by a preponderance of the evidence of record. We therefore reverse the rejections of claims 28-30, 48-50, and 54-57 under 35 U.S.C. §§ 101 and 35 U.S.C. § 112, first paragraph.

3. ANTICIPATION

Claims 28 and 48 stand rejected under 35 U.S.C. § 102(b) as anticipated by Ruggeri.[3] The Examiner finds that "Ruggeri et al. disclose a 19 residue peptide that matches SEQ ID NO: 2 at positions 704-712, a 9/15 match; see the third peptide listed in claim 1. At page 29 and in claim 65, antibodies to such peptides are disclosed and claimed." (Ans. 7.)

Appellants argue that "polypeptides are known to fold in three dimensions and the three-dimensional conformation of a polypeptide dictates which antigenic determinants are . . . exposed at the exterior of the polypeptide and capable of being bound by antibodies" (App. Br. 4). Appellants argue that antibody cross-reactivity is unpredictable and "technically uncertain" because of the different flanking amino acids in PRO285 and the prior art peptide (*id.* at 4-5). Finally, Appellants argue that the Examiner's conclusion that the antibodies would be more likely than not

[3] Ruggeri et al., WO 91/09614, published July 11, 1991.

to cross-react demonstrates that the "anticipation rejection is based upon conjecture" and therefore Ruggeri does not support the rejection (*id.* at 6-7).

In response, the Examiner cites a reference submitted by Appellants during prosecution,[4] which the Examiner refers to as "Exhibit C." The Examiner points to the reference's disclosure that

> although antibodies raised against fragments generally have higher affinities for the fragment to which they were raised than to the native protein, (page 247) they nonetheless "show extensive cross-reactions with native proteins" (page 248). Further, at page 249, the reference goes on to state that "antipeptide antibodies have proved to be very powerful reagents", and can be used to immunoprecipitate previously unisolated native proteins.

(Ans. 9.) The Examiner concludes that "the reference provided by applicants teaches that one would reasonably expect an antibody raised against Ruggeri's peptide to bind to PRO285" (*id.*).

We agree with the Examiner that the evidence of record supports a reasonable expectation that the antibodies disclosed by Ruggeri would bind to PRO285. Appellants do not dispute that Ruggeri discloses a peptide that includes nine contiguous amino acids that exactly match the sequence of part of PRO285, or that Ruggeri discloses antibodies to the peptide. But Appellants do take issue with the Examiner's conclusion that such an antibody would reasonably be expected to bind to PRO285.

In our view, the evidence of record adequately supports the Examiner's conclusion. The "Exhibit C" reference (Fundamental Immunology) states that, "[i]n light of the conformational differences

[4] The reference is identified by Appellants as "pages 242-252 of FUNDAMENTAL IMMUNOLOGY (3rd Ed. Raven Press) which are attached . . . as Exhibit C" (Response filed Dec. 9, 2003, p. 6).

between native proteins and peptides . . . it was somewhat surprising to find that antibodies to synthetic peptides show extensive cross-reactions with native proteins" (Fundamental Immunology 248, left-hand column). It also states that "the binding of antipeptide antibodies to the protein is quite efficient and commonly observed" (*id.*) and that "[a]ntipeptide antibodies have proven to be very powerful reagents" for, among other things, immunoprecipitating or isolating the native protein (*id.* at 249, left-hand column), further confirming that antibodies to a peptide will bind to an intact protein.

We agree with the Examiner that the Fundamental Immunology reference provides a reasonable basis for concluding that the antibodies disclosed by Ruggeri would bind to PRO285. The Examiner properly shifted the burden to Appellants to rebut that conclusion. *See In re Best*, 562 F.2d 1252, 1255 (CCPA 1977)("[W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on."); *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990)("[W]hen the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.").

Appellants have argued that the amino acids of PRO285 that match the sequence of Ruggeri's peptide are not necessarily on the surface of the native protein and therefore there can be no certainty that Ruggeri's

antibodies would cross-react with PRO285 (Br. 4-7). Complete certainty, however, is not the appropriate standard of proof. If the Examiner's conclusion is supported by a preponderance of the evidence of record, the burden is properly shifted to Appellants to rebut it. *See In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992) (After a prima facie case has been made out and "evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument.").

In this case, PRO285 and the prior art peptide share a sequence of nine contiguous amino acids, which is long enough to form an epitope recognized by an antibody. When we combine the length of the shared sequence with the disclosure in Fundamental Immunology that antipeptide antibodies "commonly" bind to native proteins, "show extensive cross-reactions," and are "very powerful reagents" for isolating the native proteins, we conclude that a preponderance of the evidence of record favors the Examiner's position rather than Appellants'. We affirm the rejection of claims 28 and 48 as anticipated by Ruggeri.

4. OBVIOUSNESS

Claims 29 and 49 stand rejected under 35 U.S.C. § 103 as obvious in view of Ruggeri and Coughlin.[5] Claims 50 and 54 stand rejected under 35 U.S.C. § 103 as obvious in view of Ruggeri, Coughlin, and Ladner.[6]

The Examiner relies on Ruggeri for the disclosure of antipeptide antibodies, discussed above. The Examiner cites Coughlin for its disclosure of methods of making monoclonal antibodies, as recited in claims 29 and 49

[5] Coughlin, U.S. Patent 5,256,766, issued Oct. 26, 1993.
[6] Ladner et al., U.S. Patent 4,946,778, issued Aug. 7, 1990.

(Answer 7-8), and cites Ladner for "the construction of single chain antibodies," as recited in claims 50 and 54 (*id.* at 8). The Examiner concludes that it would have been obvious to modify Ruggeri by making the disclosed antipeptide antibodies in the form of the well-known monoclonal or single-chain antibodies (*id.* at 7 and 8).

We agree with the Examiner's reasoning and conclusion.

Appellants argue that the rejections under § 103 should be reversed for the same reason as the § 102(b) rejection (App. Br. 7). Since we have concluded that claims 28 and 48 are properly rejected under § 102(b), we also conclude that Appellants have not adequately rebutted the rejections under § 103. We therefore affirm the rejection of claims 29, 49, 50, and 54 under 35 U.S.C. § 103.

SUMMARY

We reverse the rejection based on lack of patentable utility but affirm the rejection of claims 28 and 48 as anticipated by Ruggeri and the rejections of claims 29, 49, 50, and 54 as obvious in view of the cited references.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

FREDMAN, *Administrative Patent Judge*, concurring in part and dissenting in part.

I concur with the majority's analysis on anticipation and obviousness. However, I respectfully dissent from the majority's conclusion with regard

to the utility and enablement rejections under 35 U.S.C. § 101 and 112, first paragraph. I would affirm the utility and enablement rejections of claims 28-30, 48-50, and 54-57 because I feel that application of the utility caselaw to the evidence of record supports a conclusion that these claims lack utility.

In *Fisher*, the Federal Circuit recognized a distinction "between a substantial utility, which satisfies the utility requirement of § 101, and an insubstantial utility, which fails to satisfy § 101." *In re Fisher*, 421 F.3d 1365, 1372 (Fed. Cir. 2005). In *Brenner*, the Supreme Court found that an adjacent homologue of a steroid had insubstantial utility, based in part since the "Patent Office held that, despite the reference to the adjacent homologue, respondent's papers did not disclose a sufficient likelihood that the steroid yielded by his process would have similar tumor-inhibiting characteristics." *Brenner v. Manson*, 86 S.Ct. 1033, 1040 (1966).

The logic of Brenner applies to the instant facts as well. I do not think that the evidence presented provides a sufficient likelihood that antibodies to PRO285 (referred to hereafter as TLR7) will be capable of treating sepsis by downregulating TLR7 activity. The Majority relies upon a chain of evidence, the first link of which is that a partially conserved region of TLR2 is shown to be necessary for NF-κB activating function. The Majority then links that function of TLR2 to all TLR proteins in order to support the utility of the claimed protein, TLR7, as sharing the NF-κB activating function. As a final link to reach a "substantial utility", the Majority finds that even though the ligand for TLR7 is unknown and the function of TLR7 is unknown, the linkage with NF-κB provides a preponderance of evidence

that antibodies to TLR would have "substantial utility" in sepsis and inflammatory response to a pathogen.

Link 1 - Does a preponderance of evidence show that TLR7 activates NF-κB?

The Majority relies heavily on the Declaration of Dr. Bazan, and his conclusions that the skilled artisan would recognize that TLR7 can induce the activation of NF-κB and/or the expression of NF-κB-controlled genes as well as the "striking similarity" shown in the alignment of Il-1R, TLR7 and TLR2 over a 13 amino acid stretch in Exhibit B of the Bazan declaration (Bazan at ¶ 5). The Majority points to Rock and comments "[t]he amino acids indicated by Rock to be the sites of "deleterious mutations" are the same ones that are described as "essential for IL-1R signaling" in the Specification" (Maj. Opin. at 6).

I am also not persuaded by Appellants argument that "the utility of the claimed anti-TLR7 antibodies is based for example upon the Appellants' understanding that TLR7 polypeptide signaling modulates NF-κB activity and that antibodies for this receptor can modulate this activity" (Rep. Br. 8). In fact, Appellants have not shown that TLR7 modulates NF-κB activity in their specification, only that TLR2 does so (Spec. 51:1-2). Appellants have not shown that TLR7 induces interleukins and Appellants have not shown that TLR7 has any effect on pathologies such as septic shock or warts.

The alignment of figure 7b of Appellant's specification is reproduced below.

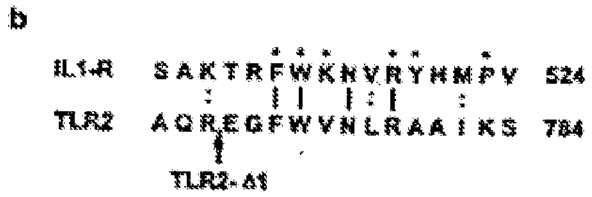

Figure 7b shows 16 amino acids at the c-terminal end of IL1-R aligned to the TLR2 sequence, and shows that there are four perfect matches and three "conservative" substitutions. However, the figure does not show how TLR7, the molecule to which antibodies are actually being claimed, would align with this region. An alignment of TLR7 with TLR2 and IL1-R in the same region is shown in Appellants Exhibit B. However, this exhibit fails to display the 14 additional amino acids of TLR7 that are C-terminal of the aligned region. No "striking similarity" is found. Only two of the amino acids shared between TLR2 and IL-1R are also shared between TLR2 and TLR7 along with three shared conservative substitutions. The low level of shared homology in this region between IL1-R, TLR2 and TLR7, particularly with the with the additional 14 amino acids present in TLR7, does not support a conclusion that TLR7 will more likely than not have the same capacity to activate NF-κB and induce an response to sepsis. Claim 55 is drawn to an antibody to TLR7, not to TLR2, and there is no evidence that TLR7 functions to activate NF-κB.

Link 2 - Does a preponderance of evidence show that all TLR proteins activate NF-κB?

Further, I find that the evidence does not support the assumption that simply because TLR2 and TLR4 activate NF-κB and induce of expression of NF-κB-controlled genes like IL-1, IL-6, and IL-8, TLR7 will predictably do the same. For example, the Specification identifies a preferred activity of TLRs such as TLR7 is "the ability to mediate lipopolysaccharide (LPS) signaling" (Spec. 13:20). The Specification demonstrates that TLR2 mediates LPS signaling (Spec 48:14-39). Applying the logic of the Majority, in which a short region of alignment indicates identical function, TLRs such as TLR3 should be useful as having the ability to mediate LPS signaling since Du shows regions of homology between TLR3 and TLR4 (Du at 366, fig. 2). However, Jurk demonstrates that this is not the case (*see* Jurk at 499). While TLR4 does recognize LPS, other TLRs have different ligands including TLR3 which recognizes double stranded RNA (Jurk at 499). Just as short regions of homology at the amino terminal end do not support a conclusion that the TLRs share ligands; a short region of homology near the C terminal end does not make it more likely than not that TLRs activate NF-κB and induce of expression of NF-κB-controlled genes like IL-1, IL-6, and IL-8. As the *Joly* court noted,

> [i]t is not enough that the specification disclose that the intermediate exists and that it 'works,' reacts, or can be used to produce some intended product of no known use. Nor is it enough that the product disclosed to be obtained from the intermediate belongs to some class of compounds which now is, or in the future might be, the subject of research to determine some specific use.

In re Joly, 376 F.2d 906, 908 (C.C.P.A. 1967).

The Majority also argues that "Dr. Bazan states that he was a co-author of a paper that compared the sequences of TLRs1-5 and that noted that the finding that TLR4 activates NF-κB was expected based on the homology data (*id.* at ¶¶ 6, 7)" (Maj. Opinion at 5). The Rock paper, referenced by Dr. Bazan, never directly suggests that TLR4 activates NF-κB based upon homology and does not identify this function until the last comment on page 593, included after the manuscript was submitted (Rock at 593). In fact, the Rock paper states that "[i]t is not known whether TLRs can productively couple to the IL-1R signaling machinery or whether a parallel set of proteins is used (Rock at 591). Rock further notes "the functions of the Toll TH domain and Tube remain enigmatic" (Rock at 591, where TH stands for Toll homology). Rock expressly recognizes that "the TH domain may capture cations in its acidic nest, but activation – and downstream signaling – could depend on the specific binding of a negatively charged moiety" (Rock at 592). Rock evidences what is well known, which is that binding and signal transduction even by homologous receptors can result in different and enigmatic effects.

Link 3 – Does a preponderance of evidence demonstrate that antibody treatment of TLR7 will treat sepsis or inflammation?

I disagree with the Majority's statement that "the Examiner's focus on whether the natural ligand of TLR7 is known (Ans. 3-4) misses the mark" (Maj. Opin. at 7). I think that this is the central question of "substantial utility" for TLR7. I also disagree with the Majority's conclusion that "those skilled in the art would expect that down-regulating the activity of a TLR family member like TLR7 would be useful in treating sepsis regardless of which specific pathogen-specific product is triggering the body's reaction." (Maj. Opin. at 7).

Without knowledge of the ligand, downregulation of TLR7 may have no effect on sepsis. In fact, Jurk shows that TLR 2 recognizes peptidoglycan, TLR4 recognizes lipopolysaccharide, TLR6 recognizes lipoproteins from mycoplasma while TLR3 responds to double stranded RNA (Jurk at 499). This suggests that TLR2 responds to infections of gram positive organisms, while TLR4 responds to gram negative infections, TLR6 responds to mycoplasma infections and TLR3 responds to infections by double stranded RNA viruses. Consequently, the skilled artisan would not expect that downregulating the activity of TLR3, responsive to double stranded RNA, would have any effect on sepsis caused by gram positive organisms.

In the same way, I think that the skilled artisan reading Jurk, who teaches that years after Appellants specification was filed the natural ligand of TLR7 is still not known (Jurk at 499), would find treatment of sepsis as an "insubstantial utility" for antibodies to TLR7 since there is no expectation

or knowledge of when such treatment would be expected to yield any tangible benefit to any patient. This case is several steps removed from the situation in *Brana*, where evidence of in vivo antitumor activity was demonstrated. *See In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). In Brana, "one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models . . . An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the courts in *Kirk* and *Kawai*." *Brana*, 51.3d at 1565. I contend that the proposed use of a TLR7 antibody against some unknown organism or ligand to prevent inflammation or sepsis is closer to a vaguely intimated use than to evidence of a compound shown to be effective in a tumor model and lacks "substantial utility".

Conclusion

I believe that the Examiner satisfied her burden of providing evidence that TLR7 lacks substantial utility. As the Examiner noted

> The Jurk paper goes on to state that 'The natural ligands for TLR1, TLR7, TLR8 and TLR10 are not known, although a synthetic compound with antiviral activity has not been described as a ligand for TLR7'. Thus, even four years after the filing date of the instant application, the role of TLR7, aka TLR7, was unknown, and the receptor was merely a subject for further research. This paper supports the Examiner's position that there is no specific, substantial and credible utility upon the protein, nor upon antibodies that bind to it.

(Ans. 5.) This is specific evidence which shows that even after the disclosure of TLR7 (TLR7), no substantial use for the molecule had yet been identified, much less for antibodies to TLR7. The Examiner also notes that

the Rock paper identifies two possible roles for TLRs, the role in immunity discussed at length by the Majority and "[i]ntriguingly, the evolutionary retention of TLRs in vertebrates may indicate another role- akin to Toll in the dorsoventralization of the *Drosophila* embryo- as regulators of early morphogenetic patterning" (Ans. 15). I agree with the Examiner's conclusion that "based upon the Rock paper, it would seem that it was not predictable that TLR7 was involved in innate immunity via signaling via NF-κB" (Ans. 15).

I do not disparage the efforts that went into identifying the TLR7 protein sequence. However, in the absence of further efforts such as those performed for TLR2, which identified the receptor's ligand and demonstrated the pathway by which the receptor operated, I think that simply identifying a protein with homology to other known proteins does not provide a "substantial utility" for antibodies to that protein. "But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. '(A) patent system must be related to the world of commerce rather than to the realm of philosophy." *Brenner,* 86 S.Ct. at 1042.

I think that granting a patent to the current Appellants for antibodies to TLR7 would amount to a hunting license because the only current use of antibodies to TLR7 is as a tool for further research into the function of TLR7. These antibodies do not have any "substantial utility" but can only be used to assist in further research into the function of TLR7. There is no "immediate, well-defined, real world benefit to the public meriting the grant of a patent." *Fisher*, 421 F.3d at 1376.

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